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EXAMINER

SULLIVAN, DANIEL M

ART UNIT

PAPER NUMBER

1636

DATE MAILED: 03/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/646,807

Applicant(s)

GRAHAM ET AL.

Examiner

Daniel M Sullivan

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 December 2002.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 and 43-47 is/are pending in the application.
- 4a) Of the above claim(s) 14-16, 19-26, 29-33 and 39 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-13, 17, 18, 27, 28, 34-38, 40, 43 and 47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 05 December 2000 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 7, 16.
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

This is a First Office Action on the Merits of the application filed as the U.S. National Stage of international application PCT/AU99/00195 filed 19 March 1999, which is a continuation in part of U.S. application No. 09/100,812 filed 19 June 1998, which is a continuation in part of U.S. application No. 09/100,813 filed 19 June 1998 and claims benefit of Australian applications PP 2492 filed 20 March 1998 and PP 2499 filed 20 March 1998. The preliminary amendments filed 5 December 2000 (Paper No. 6), 14 May 2001 (Paper No. 8) and 2 August 2001 (Paper No. 9) have been entered in the case. This Office Action is a response to the "Response under 37 C.F.R. §1.111 and 1.143 filed 24 December 2002 (Paper No. 18). Claims 1-40 and 43-47 are pending in the application.

Election/Restrictions

Applicant's election with traverse of Group I (claims 1-13, 17, 18, 27, 28, 34-38, 40, 43 and 47) in Paper No. 18 is acknowledged. The traversal is on several grounds.

First, Applicant disagrees with the Examiner's assertion that the method of suppressing target gene expression does not represent a contribution over the prior art. Applicant states that it is not clear as to which references the Examiner is referring as to allegedly providing a teaching for a method of suppressing target gene expression by introduction of nucleic acid molecules comprising tandem copies of a nucleotide sequence that is identical or complementary to the nucleotide sequence of a target gene, but that, in any event, no prior art teaches suppression of target gene expression in animal cells. This argument is not persuasive because the limitation to animal cells or target genes comprised within animal genomes or the genome of animal viruses is

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not a technical feature of all of the claims. For example, claim 27 encompasses a synthetic gene comprising a nucleic acid molecule which is substantially identical to any target gene regardless of the kingdom of origin of that target gene. Therefore, any of the X references cited against the international application reads on the special technical feature of a method of suppressing target gene expression by introduction of nucleic acid molecules comprising tandem copies of a nucleotide sequence that is identical or complementary to the nucleotide sequence of a target gene. Further, even assuming, *arguendo*, the special technical feature is limited to animal cells, it does not represent a contribution over the prior art as evidenced by the publications cited below under "Claim rejections-35 U.S.C. § 102".

Next, Applicant argues that the Examiner's assertion that the method of Group I, directed to suppression of endogenous genes within an animal cell, differs in both function and effect from the method of Group II, which is directed to suppression of genes comprised within the genome of a pathogenic organism, is in error. Applicant asserts that the methods of each group are directed toward achieving the same function and effect-i.e., suppression of the target gene expression in the animal cell. Further, Applicant asserts that the method of Group I and method of Group II are achieved by essentially the same mechanism. This argument has been fully considered but is not found persuasive because, to the extent that the claims are directed to inhibiting expression of an endogenous gene or a gene derived from a pathogen, the effect would be to suppress completely different genes. Therefore, although the mechanisms might be the same when considered in a broad sense, to the extent that claims are directed to inhibiting expression of genes derived from completely different organisms, they are distinct. That is, the method of Group I would clearly not work to reduce expression of a gene derived from the

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genome of a pathogen and *vice versa*. Therefore, the mechanisms must be different.

Furthermore, as stated in the previous office action, the function and effect of the method of Group I could be to suppress neoplastic cell growth by inhibiting expression of an oncogene, while the function and effect of the method of Group II is limited to inhibiting expansion or toxicity of a pathogen. This is also evidenced by the fact that Group II embraces methods such as claim 19, directed to conferring resistance or immunity to a viral pathogen, which are clearly not a function or effect of the method of Group I. Therefore, the methods of Groups I and II have distinct application, and thus different function and effect.

Applicant expresses concern regarding the consequences of improper imposition of a restriction requirement. However, for the reasons provided above, the restriction requirement is not improper and, therefore, the concerns expressed are not relevant to the instant case.

Finally, Applicant submits that a determination to make the pending restriction requirement final must evidence the patentable distinctness of the defined two groups, one from the other, as presented by the Examiner. The examiner submits that, absent evidence to the contrary, the reasons provided above, which demonstrate the distinct function and effect of Groups I and II, are adequate evidence of the patentably distinct nature of the Groups.

The requirement is still deemed proper and is therefore made FINAL.

Claims 14-16, 19-26, 29-33, 39, 41 and 42 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claim Rejections - 35 USC § 101

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35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 43 and 47 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claims, as they are directed to a whole organism comprising a synthetic gene, encompass a genetically modified human, which is not patentable subject matter. Amending the claims such that they are directed to a non-human organism would obviate this rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13, 17, 18, 43 and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of repressing, delaying or otherwise reducing the expression of a target gene contained within the genome of an animal cell *in vitro* and an animal cell *in vitro* comprising a synthetic gene or genetic construct according to claims 27 or 38, respectively, does not reasonably provide enablement for the method *in vivo* or a tissue, organ or whole organism comprising the synthetic gene or genetic construct according to claims 27 and 38, respectively. The specification does not enable any person skilled in the art to which

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it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (a) the nature of the invention; (b) the breadth of the claims; (c) the state of the prior art; (d) the amount of direction provided by the inventor; (e) the existence of working examples; (f) the relative skill of those in the art; (g) whether the quantity of experimentation needed to make or use the invention based on the content of the disclosure is "undue"; and (h) the level of predictability in the art (MPEP 2164.01 (a)).

Nature of the invention: The elected invention is directed to a method of repressing, delaying or otherwise reducing the expression of a target gene contained within the genome of an animal cell, tissue or organ comprising introducing into said animal cell, tissue or organ one or more dispersed or foreign nucleic acid molecules comprising tandem copies of a nucleotide sequence identical to or complementary to the nucleotide sequence of said target gene or a region thereof. Additional claims are directed to products used in or made by the method. The disclosure provides that the method is generally useful for producing novel traits in a particular cell, tissue or organ (see for example page 4, paragraph 1 and page 6 paragraph 3). In addition, Example 9 (beginning page 70) and claims 13, 34, 35 and 40 indicate that the invention is useful for suppression of α -1,3-galactosyl transferase. Although the instant specification does not state a purpose for suppression of α -1,3-galactosyl transferase expression, it is known in the art that

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the enzyme is required for expression of the major antigen responsible for hyperacute, antibody mediated rejection of xenografts.

Breadth of the claims: The claims encompass a method of repressing, delaying or otherwise reducing the expression of any gene comprised within the genome of an animal cell, tissue or organ. Based on the teachings of the specification, the claims relate to a method of making a cell, tissue or organ having novel traits and specifically having reduced expression of α -1,3-galactosyl transferase, the only patentably useful purpose of which is xenotransplantation.

State of the prior art and Level of predictability in the art: First, with respect to obtaining a useful product *in vivo* according to the instant method, the art of record at the time of filing provides only one example of gene suppression in an animal (i.e. *C. elegans*) *in vivo* (see Fire (1999) *Trends. Genet.* 15:358-363). In the section entitled “**Real-world applications: what about us?**” Fire goes on to teach “[f]rom a technical perspective, one could certainly hope that RNA-triggered silencing would exist in vertebrates: this would facilitate functional genomics and might allow medical applications involving targeted silencing of ‘renegade’ genes. Although this hope is not ruled out by any current data, the simple protocols used for invertebrate and plant systems are unlikely to be effective. Mammals have a vehement response to dsRNA, the best-characterized component of which is a protein kinase (PKR) that responds to dsRNA by phosphorylating (and inactivating) translation factor EIF2a...Controlled-delivery studies suggest that a single molecule of dsRNA within the cell can trigger an overall cellular response. Any gene-specific dsRNA response in mammals would need to exist in cells or conditions where PKR is less effective, or would need to work in the shadow of the PKR-induced global response” (paragraph bridging pages 362 and 363). These teachings demonstrate the high degree of

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unpredictability that existed at the time of filing regarding extending results obtained in *C. elegans* to higher organisms. Fire clearly teaches that even if success is eventually obtained in higher organisms, it will require development of new protocols and thus will not be accomplished by routine experimentation.

Additional basis for unpredictability is found in teachings from the antisense art. Dietz (U.S. Patent No. 5,814,500) teaches that many studies with antisense show that gene expression is suppressed by 80%-90% of the normal level, but that such reduction is not typically sufficient to reduce the biological effect, i.e., 10%-20% expression is sufficient to maintain the biological function sought to be suppressed. Thus it is not a routine matter to design molecules appropriate to induce the degree of inhibition necessary to produce the desired effect. Accordingly, the *in vivo* effect of any particular method of post-transcriptional suppression of a gene product cannot be predicted. Furthermore, the operability of the claimed method *in vivo*, in any animal, depends on a number of factors beyond those stated above. Good *et al.* (1997) *Gene Ther.* 4:45-54 teaches that the effective intracellular expression of small RNA therapeutics requires that the RNA be efficiently transcribed, stabilized against rapid degradation, folded correctly, and directed to the part of the cell where it can be most effective (Abstract). The specification does not provide specific guidance for inhibiting the expression of any gene *in vivo*; thus, the specification does not teach how to produce a desired effect *in vivo* using the instant method. Furthermore, in the absence of specific guidance regarding the design of a nucleic acid molecule to produce the desired effect (i.e. suppression of any gene *in vivo* such that a useful product is obtained), one skilled in the art would not know how to make the compositions necessary for use in the claimed method.

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With regard to the use of the claimed method for the purpose of preparing organs for xenotransplantation, the prior art teaches that the problem of preparing an organ suitable for xenotransplantation is extraordinarily complex and that the art of xenotransplantation is highly unpredictable. In a recent article McKenzie et al. (Transplantation (1999) 827-874. Editor(s): Ginns, Leo C.; Cosimi, A. Benedict; Morris, Peter J. Blackwell Science, Inc.: Malden, Mass.) teach that there are many hurdles to be overcome in achieving a successful xenograft including hyperacute, delayed and cellular rejection and species incompatibility of organs. The teachings of the instant application provide a method for reducing expression of Gal α (1,3)Gal in an organ. However, McKenzie teaches that “[a]s the major problem in pig-to-primate grafts is HAR [hyperacute, antibody-mediated rejection] due, predominantly, to the Gal α (1,3)Gal antibody, major efforts are being directed to the reaction of these antibodies and to complement. When this problem is overcome, [delayed xenograft rejection], cellular reactions, and other molecular problems will need to be addressed as they arise” (page 854, second full paragraph); “[o]nce HAR can be avoided, the stage will be set to examine other procedures such as delayed graft rejection, chronic rejection and other problems...Whether this will suffice for permanent graft survival cannot be predicted at this stage; our optimism can extend only to short-term grafts of days or weeks” (beginning the final paragraph on page 865 and continuing through the first paragraph on page 866); “cells from [Gal α (1,3)Gal]-deficient mice still bind to other natural human antibodies...Thus, gene inactivation of the α 1,3galactosyltransferase [leading to reduced Gal α (1,3)Gal] alone is not the ultimate solution to the production of the universal donor pig” (page 859, second column, first paragraph); α -galactosidase transgenic pigs, while having decreased Gal α (1,3)Gal, would still express “uncapped” *N*-acetyl lactosamine residues that

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could bind human antibodies and lead to HAR” (page 859, column 2, first full paragraph). These teachings demonstrate that reducing Gal α (1,3)Gal expression is only a first step in producing an organ suitable for xenotransplantation and that successfully traversing the problems of producing an organ suitable for xenotransplantation beyond preventing HAR is highly unpredictable.

Amount of direction provided by the inventor and existence of working examples: The instant disclosure provides a general description of methods of introducing nucleic acids into cells and specific examples of constructs that can be used in the methods to suppress gene expression. In addition, Example 9 provides a prophetic example of inactivation of the α -1,3-galactosyl transferase using the described method and constructs. The specification does not teach a single working example of the claimed invention and is silent with regard to how the unpredictability that existed in the art at the time of filing would be overcome by the instant claimed product and methods. The instant disclosure essentially describes a nucleic acid construct and method of putting that nucleic acid construct into a cell, and states that a useful degree of repression of gene expression will occur without regard to the many art recognized hurdles that lie between introduction of the nucleic acid construct into the cell and the desired outcome. The disclosure therefore fails to teach the skilled artisan how to make or use the claimed invention as it is directed to a method of repressing, delaying or otherwise reducing the expression of a target gene in an animal cell, tissue or organ *in vivo*.

Relative skill of those in the art and quantity of experimentation needed to make or use the invention: Although the relative level of skill in the relevant art is high, given the very high level of unpredictability in the art and the absence of any teaching in the disclosure to indicate that the instant method has addressed the sources of unpredictability, the skilled artisan would

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not be able to make or use the instant claimed products and methods without first engaging in undue experimentation.

Claims 27, 28, 36-38, 43 and 47 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a synthetic gene or genetic construct which is capable of delaying, repressing or otherwise reducing the expression of a target gene in an animal cell into which said synthetic gene or genetic construct has been introduced and an animal cell comprising the synthetic gene or genetic construct, does not reasonably provide enablement for *any* and *all* synthetic genes or genetic constructs comprising a dispersed or foreign nucleic acid molecule comprising tandem copies of a nucleotide sequence which is substantially identical to the nucleotide sequence of said target gene or a derivative thereof or a complementary sequence thereto placed operably under the control of a promoter sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claims are directed to synthetic genes or genetic constructs having structural limitations but no functional limitations. The specification discloses that such constructs can be used to produce novel traits in a particular cell, tissue or organ by suppression of target gene product expression. However, the relevant art, exemplified by Selker (1999) *Cell* 97:157-160, teaches that suppression of target gene expression is not predictably tied to the structure set forth in the claims. Selker teaches, “[s]ingle-copy sequences can experience PTGS even in haploid cells; thus, while commonly repeat associated, PTGS is not repeat induced...Not all sequences appear capable of triggering PTGS...Not every transformant bearing PTGS-susceptible sequence

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shows silencing, even when multiple copies of the DNA are present” (first column on page 158). Therefore the claims clearly encompass synthetic genes and genetic constructs that would not function to delay, repress or otherwise reduce the expression of a target gene in an animal cell into which it is introduced. As there is no guidance in the specification or prior art that teaches how the skilled artisan should use synthetic genes or genetic constructs having the structural limitations set forth in the claims which do not function to delay, repress or otherwise reduce the expression of a target gene, the skilled artisan would have to engage in undue experimentation to divine a practical use for such constructs.

Claims 34, 35 and 40 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The claims are directed to a synthetic gene or genetic construct comprising tandem repeats of the α -1,3-galactosyl transferase gene. The specification does not disclose a real world utility for the claimed product. Although the art teaches that the products might be useful for preparing organs and tissues for xenotransplantation, for the reasons provided above, the skilled artisan would not be able to use the constructs for that purpose without first engaging in undue experimentation. Therefore, the claims are not enabled over any scope.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11, 27, 28, 34-38, 40, 43 and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is indefinite in its recitation of “the animal” in line 1. There is no antecedent basis for “the animal” in claim 1 which is directed to suppression of expression in an animal cell, tissue or organ. Amending the claim such that it is directed to the method of claim 1 wherein the animal cell tissue or organ is a mouse cell tissue or organ would obviate this rejection.

Claim 27, and claims 28, 34-38, 40, 43 and 47 as they depend therefrom, are indefinite in being directed to derivatives of the target gene. The specification defines “derivatives” as any isolated nucleic acid molecule which contains significant sequence similarity to said nucleotide sequence or part thereof. The metes and bounds of the limitation are unclear because the specification provides no objective measure of “significant sequence similarity”. It is therefore impossible to tell what is encompassed by a derivative of a target gene.

Claim 28 is additionally indefinite in its recitation of “the animal cell, tissue, organ or organism”. There is no antecedent basis for this limitation in claim 27, from which claim 28 depends.

Claim 35 is additionally indefinite in being directed to the synthetic gene according to claim 24, while claim 24 is directed to a method. In the interest of compact prosecution, it is assumed that applicant intends that claim 35 depend from claim 34.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

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improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 27 and 38 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 2 of copending Application No. 09/100,812. Claims 43 and 47 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 38 of copending Application No. 09/100,812. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claim 27 is directed to a synthetic gene comprising a dispersed or foreign nucleic acid molecule comprising tandem copies of a nucleotide sequence which is substantially identical to the nucleotides sequence of said target gene or a derivative thereof or a complementary sequence thereto placed operably under the control of a promoter, and claim 38 is directed to a genetic construct comprising the synthetic gene according to claim 27. Claim 2 of 09/100,812 is directed to an isolated genetic construct which is capable of delaying, repressing or otherwise reducing the expression of a target gene in an animal cell which is transfected with said genetic construct, wherein said genetic construct comprises at least two copies of a structural gene sequence, wherein said structural gene sequence comprises a nucleotide sequence which is substantially identical to at least a region of said target gene, and wherein said at least

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two copies of said structural gene sequence are placed operably under the control of a single promoter sequence which is operable in said cell, wherein at least one copy of said structural gene sequence is placed operably in the sense orientation under the control of said promoter sequence.

The limitations of claim 2 of 09/100,812 are completely encompassed within the limitations of the instant claim 27. Thus, claim 27 merely expands the scope of claim 2 in a nonspecific manner. The limitations of the instant claim 27 would therefore be obvious to one of ordinary skill in the art in possession of claim 2. Likewise, the animal cell comprising the synthetic gene according to claim 27 or the genetic construct according to claim 38 to which claims 43 and 47, respectively, are directed, would have been obvious to the ordinary skilled artisan in possession of claim 38 of 09/100,812 for the reasons provided above.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 27, 28, 36 and 37 are rejected under 35 U.S.C. 102(b) as being anticipated by Dorer *et al.* (1994) 77:993-1002 (made of record in the IDS filed 14 May 2001).

Dorer *et al.* teaches a synthetic gene (as the term is defined on page 27 of the specification) comprising a dispersed nucleic acid molecule (as the term is defined on page 20 of the specification) comprising tandem copies of a nucleotide sequence which is substantially identical to the nucleotide sequence of the mini-*white* target gene placed operably under the control of a promoter sequence (see especially Figure 3 and the caption thereto). The synthetic gene taught by Dorer *et al.* thus meets all of the limitations of claim 27. Dorer *et al.* further teaches: a synthetic gene according to claim 27 comprising tandem inverted and/or direct repeats of a genetic sequence that is endogenous to the genome of an animal (i.e. *Drosophila*) cell according to claim 28 (see especially Table 1) and tandem copies of the nucleotide sequence operably linked to spatially separate promoter sequences according to claims 36 and 37 (Figure 3). The synthetic gene taught by Dorer *et al.* is the same as the synthetic gene taught in the instant application, therefore the claims are anticipated by Dorer *et al.*

Claims 1, 2, 12, 17, 18, 27, 28, 38, 43 and 47 are rejected under 35 U.S.C. 102(e) as being anticipated by Fire *et al.* (U.S. Patent No. 6,506,559).

Fire *et al.* teaches a method of repression, delaying or otherwise reducing the expression of a target gene in an animal cell or tissue comprising introducing a dispersed nucleic acid molecule comprising a nucleotide sequence identical and complementary (i.e. double stranded) to the nucleotide sequence of a target gene or region thereof wherein the nucleic acid molecule is introduced for a time and under conditions sufficient for translation of the mRNA product of said

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target gene, wherein transcription of said mRNA product is not exclusively repressed or reduced (see especially “Description of the dsRNA Inhibition Phenomenon in *C. elegans*” beginning at column 14; the second full paragraph in column 4; and the third full paragraph in column 6). Fire *et al.* further teaches, “[t]he double stranded structure may be formed by a single self-complementary RNA strand” (third full paragraph in column 7) and thus a nucleic acid comprising at least one tandem inverted repeat. Therefore, the method taught by Fire *et al.* meets the limitations of claims 1 and 2.

In the fourth full paragraph in column 6, Fire *et al.* teaches that the target gene may be a gene derived from the cell (i.e. cellular gene) according to claim 12. In the second full paragraph in column 4, Fire *et al.* teaches that the nucleotide sequence from a portion of the target gene is chosen to produce inhibitory RNA, and thus to effectively repress, delay or reduce expression of the target gene according to claim 17 and 18. Furthermore, selection of a nucleic acid that is functional in the method of repressing, delaying or reducing expression of a target gene is inherent to any such method.

The dispersed nucleic acid molecule comprising a double stranded structure which may be formed by a single self-complementary RNA strand and thus at least one tandem inverted repeat taught by Fire *et al.*, and described herein above, meets the limitations of synthetic gene of claim 27 and 28. Further, in the paragraph bridging columns 8 and 9, Fire *et al.* teaches that the double stranded RNA may be synthesized *in vivo* from a transgene or expression construct which meets the limitations of the genetic construct of claim 38. Finally, in the paragraph bridging columns 4 and 5, Fire *et al.* teach that the synthetic gene or genetic construct can be comprised within an animal cell, which meets the limitations of claims 43 and 47. The products and

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methods taught by Fire *et al.* meet all of the limitations of the instant claims; therefore, the claims are anticipated by Fire *et al.*

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Daniel M Sullivan whose telephone number is 703-305-4448. The examiner can normally be reached on Monday through Friday 8-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel, Ph.D. can be reached on 703-305-1998. The fax phone numbers for the organization where this application or proceeding is assigned are 703-746-9105 for regular communications and 703-746-9105 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

dms
March 6, 2003


ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER